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Three topics integral to the use of the Internet for clinical trials: Connectivity, communication, and security

Drug Information Journal; Ambler; Oct-Dec 1998; David I Hopp;

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[Headnote]
This paper discusses three somewhat arbitrarily constructed topics integral to the use of the Internet, specifically the Web, for clinical trials: connectivity, communication, and security. The discussion poses a set of considerations to be applied to each of these topics, forming a basis for realistic and successful implementation of Web-based techniques for the conduct of clinical trials.
Key Words: Internet; World Wide Web; Clinical trials; Decision framework; System implementation

THE INTERNET HAS SHOWN value in almost every field of science, art, and industry ever since the World Wide Web, invented by Andreeson, Berners-Lee and their associates in the late 1980s, left the confines of the computing community and thrust the Internet upon the everyday world. The conceptual framework for this had already been laid out in the pioneering work of Bush in 1947, and in the incisive commentary of McLuhan in the 1960s and Nelson in the 1980s (1,2). These later years of the 1990s have been for the `down and dirty' work required to realize the tantalizing potential of the Web.

The promise of the Web for clinical trials lies primarily in its ubiquity. Inexpensive Web service is available almost everywhere in North America and Europe, and is steadily becoming so in many other parts of the world. Web browsers are easy to use and easy to obtain, which to a large extent reduces the traditional problems of providing and supporting special-purpose software installed at the many locations involved in trials. The Internet, as a public infrastructure, permits the speedy and inexpensive creation of secure networks to connect trial sites, contract research organizations (CROs), sponsors, and other trial participants. This more rapid acquisition and distribution of clinical trial information provides the ability to do more in less time, and accordingly creates economic advantages for the clinical trial industry.

This paper will discuss three somewhat arbitrarily constructed topics integral to the use of the Internet, specifically the Web, for clinical trials. The first is connectivity, the ability to establish and maintain the connections that permit information to be communicated. The second is communication, the ability to make use of information. The third is security, the ability to maintain the value of information. While these overlap substantially, they are convenient containers for discussion. The discussion here will concentrate on public networks, that is, the use of the public structure of the Internet as contrasted with private networks created from leased lines and analogous technologies.

The fundamental information requirement in the conduct of clinical trials remains the same as it has been, regardless of Webs and computers. It is the need for timely, accurate, and comprehensive information available to those who require it in order to make decisions. What has changed over the past decade or two is the internationalization of trials, where participants may be scattered over time zones and regulatory authorities, and the need for increased speed of access to information in order to respond to an increasingly competitive environment.

CONNECTIVITY

It is obvious that any clinical trial participant who intends to use the Web must be connected to the Internet. It is not so obvious how to make this happen. Access to the Web, from the end user's point of view, is via a browser, such as Netscape Navigator or Microsoft Internet ExplorerT. Behind the browser lies the electronic connection to the physical Internet, however, which raises many questions.

What is the extent and nature of Internet services (Internet Service Providers or ISPs) in the particular countries? Is service available throughout the country, what are the costs, what are the connection speeds and types (standard modem, ISDN, DSL, cable, etc.), are leased or equivalent lines available?

If elements of connectivity need to be provided, how long will they take to be installed? Are there barriers created by lack of timely availability of technical assistance and telecommunications infrastructure?

If participants have their own communication infrastructure, is interconnection possible? Is encryption desired, and to what degree? Are there governmental regulations that act to inhibit utilization via tariffs, security requirements, and so forth?

How robust will the connectivity be? Will there be sufficient speed to permit the use of the kinds of applications in mind? Will reliability be substantial enough not to frustrate participants and deter practical use?

Is it reasonable to plan for interactive use or will a distributed database model be necessary? Interactive use requires reliable connectivity and quick response. In the event that connectivity is not sufficient to support real-time data entry and review, a distributed database approach could be used. In this case, each client (local) computer might have a database such as Personal Oracle(TM), and software to support the required data entry and display capabilities. Database synchronization could take place on a periodic basis determined by the nature of the trial, and would require only a brief connection to the Internet. This leads to implementation complexities and has all the difficulties associated with distributed databases,

If satisfactory connectivity is available to only some of the participants, such as selected trial sites, what will have to be done to achieve overall success in the conduct of the trial? A mixed model, where some sites have Internet access and some do not, requires planning to accommodate the consequent variety of needs. For example, central sites might enter data for subsets of the sites, while other sites may enter their own data. Careful planning will be needed to identify responsible personnel, make sure that data are forwarded to central sites on a timely basis, generate and distribute reports, and handle errors and corrections, Are there internal resources, policies and practices that inhibit the utilization of the kind of applications required for the trial? For instance, internal fire walls may degrade the speed of communications or be incompatible with security requirements, or policies regarding use of the Internet may make it difficult to provide the proper persons with access,

What are the costs? Sufficiently capable computers with the proper operating system, browser, and Internet connection must be provided, and connection and communication charges may be incurred, and What extent of technical support may be required for participants? There will need to be a plan for dealing with computer failures, and network difficulties will have to be diagnosed and fixed.

At present, the countries best outfitted for Internet connectivity are the United States and England. Canada and some of the European countries also have substantial resources. The European Union has begun the process of introducing competition in telecommunications in member countries that previously fostered telopolies, which should substantially improve the situation in Europe. The United Kingdom began deregulation in the early 1990s; Finland, Sweden, Denmark, and The Netherlands began prior to 1998; Austria, Belgium, France, Germany, Italy, Norway, and Switzerland are scheduled to begin in 1998; Spain, Ireland, Luxembourg, Portugal, and Greece will begin in 1999 or later.

Eastern Europe and the countries of the former Soviet Union generally have unreliable telecommunications. Asia has a situation that varies widely between countries, and in particular, Japan appears to have a surprising lack of reasonably priced Internet availability, mainly due to high telecommunications tariffs. Australia appears to be well

supplied. Africa and Latin America do not seem to have much in the way of such services. The Middle East is not well provided, although Israel has good facilities. Search engines (Excite, ⓘYahoo!, Hotbot, Lycos, etc.) provide a fairly good way to keep up with what facilities are available in various parts of the world.

COMMUNICATION

The most basic concern regarding communications is who needs what information, and when. While all information has time value, the scale varies greatly, and there is no point in paying excessively to handle information as though it was all of some uniform urgency. On the other hand, new opportunities emerge when information is made available in a more timely manner than is customary. Here are some examples of providing information via the Web that show advantages to be gained over more traditional methods:

Documents can be converted to a format such as Adobe(TM) Portable Document Format (PDF) and shared with participants for viewing and printing. Examples are contracts, protocols, informed consent forms, study procedure manuals, case report forms, draft reports, final reports, and so forth. The Food and Drug Administration (FDA) accepts documents in PDF format for archiving purposes and distributes PDF documents from its Web site,

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Progress of a trial at individual sites (with the proper software applications) can be reported reliably and rapidly, thus permitting better tracking of trials. This contributes to better patient care and more economical trials, and provides a better basis for developing and acting on cost metrics. Improved cost metrics can lead to improved ways of estimating trial costs and developing contracts between sponsors, CROs, and other contractors,

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Suppliers, such as those that provide CTM, can report and review information relevant to their services in a prompt and unambiguous manner, and consequently provide better service, and

Management can view reports as they are released rather than waiting for mail or fax. International trials can be better coordinated through the use of such prompt reporting.

The effectiveness of communication depends on methods of presentation, which for the present Web are determined by browsers and plug-ins, the latter being an inconvenient and awkward solution that should go the way of the hand-operated switchboard. The discipline of `Web usability' affords many recommendations and studies to assist in creating sound presentation methods (3).

The main obstacle to the use of extended browser capabilities, such as Cascading Style Sheets, Extended HTML, and so forth, is the refusal of the principal players in the browser market to agree on compatible implementations. System designers are left with the choice of ignoring advanced capabilities, maintaining multiple versions of pages for the different browsers, or restricting their audiences to only a particular browser, all of which have serious long-term disadvantages. Hopefully, there will be sufficient periodic convergence so that 'standard' capabilities can be utilized without these undue complications.

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Another aspect of communications is the mundane, yet critically important area of electronic mail. It might be thought that since e-mail is readily available (even to free e-mail being provided at the minor burden of viewing advertisements), its use in clinical trials is settled. Unfortunately, there are several obstacles. For one, not all e-mails support all types of attachments, so that for instance, large files may not be able to be exchanged by all the participants in a trial. Additionally, e-mail stands apart from the actual trial 'docubase,' that is, participants will have e-mail on their own computers and in their own varieties of e-mail, and some e-mails may be discarded, lost,

or never reach their addressees. This leaves little hope of creating a comprehensive view of the communications associated with a trial. E-mail may be nearly ubiquitous, but its utility and reliability are not sufficient to support the conduct of clinical trials. For the most part, these shortcomings can be addressed by utilizing a messaging system specifically for trials, where all electronic communications are intrinsically a part of the trial database.

One other consideration regarding communication is the number of languages and regional 'vocabularies' (such as pharmacopoeia) that need to be supported. Even when American English is acceptable, drug names, phrasing of adverse experience descriptions, and so forth, may require recognition of regional requirements.

SECURITY (4,5)

Some of the conundrums that are frequently encountered in dealing with security issues can be resolved by recognizing that Internet security has many different aspects. For one, security solutions vary widely in cost and complexity, and in some cases a simple solution can solve a substantial amount of the potential problems. For another, there are different 'domains' of security problems, such as hacker attacks on computers, capture or interference with information during transmission, theft or vandalism of information from within an organization, and so on. In any case, concerns should be carefully stated so that appropriate solutions can be brought to bear upon them. The following are some of the concerns that apply to clinical trials.

Within an organization, regardless of the Internet, information can be viewed, altered, or distributed by staff This is probably the most common and the most insidious security problem-and is basically low-tech. Solutions involve utilizing an `industrial strength' database that incorporates security privileges at a fine-grained level, and establishing corporate policies, including security audits,

A site, whether server or client, can be hacked: To a large degree, servers can be protected by firewalls or similar approaches, but vigilance is required and security procedures must be planned and enforced. A comprehensive and up-to-date source for security information is at CERT (6). Server protection is becoming automatic, in the sense of being invisible to the user, as network software acquires built-in protection capabilities. Client attacks are best avoided by putting in place procedures controlling what can be downloaded, visiting only trusted Web sites, and using Internet-virus detection software. Client protection is a weak point, however, since it is difficult to control the apparently innocuous actions of users who might inadvertently introduce viruses,

Information can be intercepted in transit (on the Internet) and used for industrial intelligence purposes: Generally speaking, clinical trial data are of low intrinsic value compared to financial data, and methods to protect them in transit need not be as complex and expensive as those utilized in electronic commerce. The Secure Sockets Layer (SSL) technology incorporated in many Web servers and browsers is quite up to handling this problem for clinical trials, and

Information can be intercepted in transit (on the Internet) and corrupted or falsified, and unauthorized persons can gain access to entering, updating, or viewing the information on a Web site via a browser: These general areas continue to receive a great deal of attention and there are many different tools commercially available to address them. These areas also present substantial conceptual problems for the nonspecialist as there is a lack of standards, and solutions tend to be targeted to particular business problems and equipment configurations. These areas can be characterized in the following ways (7):

Confidentiality: Verifying that information is accessed (read or written) only by a specific set of recipients or originators, Authentication: Identifying an individual or computer to ensure that he/it is a member of a specific set, complementary to `Confidentiality,'

Nonrepudiation: Ensuring that people cannot deny their electronic actions,

Replay prevention: Ensuring that transactions cannot be repeated,

Integrity: Verifying that information received is what was put there by the originator,

Access control: Verifying that resources are under the exclusive control of authorized parties, and ensuring that unauthorized persons are denied access, and

Availability: Ensuring that data and server resources are up and running when needed, and determining whether any downtime was caused by security-related incidents.

The Secure Virtual Private Network (SVPN) is a technology that, utilizing cryptographic techniques, creates secure

Internet communications between computers (including mobile users) and their network servers as if they were connected directly to the home network. SVPNs appear to accommodate many of the requirements discussed here in a reasonably simple and inexpensive way. At the present time, however, there are several obstacles to their adoption. One is that standards for SVPNs are not set, leading to interoperability problems reminiscent of those encountered with incompatible browsers, and another is that there may be conditions that the participants in a SVPN must satisfy. For example, a user's intervening firewall could interfere with use of SVPNs, and some SVPNs require specific operating systems on servers and client computers. Another problem is that SVPNs may introduce considerable delays in communications, resulting in the frustration of users and consequent lack of acceptance. This technology is changing rapidly and interoperability problems are becoming less substantial.

Intrusion detection and response systems capable of detecting intruders and automatically terminating the connection are beginning to appear on the market. The combination of SVPNs and intrusion detection technologies may offer a comprehensive solution as these technologies mature, but its widespread impact within an organization requires commitment from management for successful implementation.

Security is a rapidly changing part of Internet infrastructure and such emerging consumer technologies as smart cards, which are a product of the credit card industry, may have a significant impact. Within a few years the convergence of standardized smart card readers on computers, for identification, and simple to use SVPNs could very well be sufficient for the security needs of clinical trials.

ESTABLISHING DIRECTIONS

The new modality of the Web provides the opportunity for new ways of solving problems, and new opportunities for achieving business goals. Of course, no matter how attractive a technology might appear, the various participants in **clinical trials** will view it in their own terms. Utilization of the **Internet** in the **conduct** of clinical trials should be viewed within an overall information systems framework, but not as a monolithic task. The first step is to clarify strategic goals by looking at the ways in which clinical trials will be conducted and how this relates to the connectivity, communication, and security issues already discussed. Strategic goals, and the tactics to realize them, will differ among participants.

An international pharmaceutical company may have a proprietary network and a large technical staff, while a CRO may have to deal with the requirements of many sponsors concurrently. In any case, it will be necessary to identify the basic tasks and to set priorities for addressing them. It is especially important to clarify the `Internet roles' of the various participants since a lack of attention to this can lead to overcomplication, underachievement of goals, and mission failure. Some of the considerations to be addressed are:

What is the degree of persistency of the participants? There might be long term relationships to be supported, such as between a sponsor or CRO and a Phase I clinic, between a sponsor and a CRO in a preferred provider relationship, or between the sites and the central office of a site management organization. In many cases, there will short-term arrangements between a sponsor or CRO and trial sites. Short-term arrangements can require training, provisioning, and support that inhibit the use of Web-based solutions. Benefits can accrue even in short-term relationships through use of the Web for distributing reports rather than acquiring data,

Are patient data (case report forms) to be collected via the Internet? If this is considered to be source data, then there must be a high degree of attention paid to its integrity,

Are logistical data, such as enrollment and patient progress, clinical trial material consumption and restocking, financial memos, and so forth, to be handled? This kind of activity is substantially easier to implement than that of acquiring patient data, and has a high value in trial management, and

Are trial communications, such as data clarifications, monitor/coordinator e-mails, procedure clarifications, and so forth, to be handled? What is the value attached to storing all of these communications in the project database, in contrast to using conventional e-mail that may distribute communications and make a comprehensive view difficult to obtain?

Use of the Web has the potential for better cost control and more realistic budgeting due to the ease of obtaining pertinent information in a timely manner. There are considerable technical hurdles to overcome, among these being that building robust Web-based applications calls for extensive design and highly competent programmers. There have been many instances, in clinical trials and other businesses, where difficulty and resource requirements have been understated, leading to wasted time and money, and failed projects. Nevertheless, this technological opportunity, realistically handled, can lead to significant benefits.

In any case, Moore's Law, that computing power doubles every 18-24 months while price remains constant, continues to hold and today's good solution may be inefficient tomorrow. Conversely, what appears out of reach today may be commonplace tomorrow. It is possible to deal with this high rate of technological change if the underlying business needs are explicitly stated and understood, and the advantages to participants are stated in business terms.

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Within an organization, regardless of the Internet, information can be viewed, altered, or distributed by staff This is probably the most common and the most insidious security problem-and is basically low-tech. Solutions involve utilizing an `industrial strength' database that incorporates security privileges at a fine-grained level, and establishing corporate policies, including security audits,

A site, whether server or client, can be hacked: To a large degree, servers can be protected by firewalls or similar approaches, but vigilance is required and security procedures must be planned and enforced. A comprehensive and up-to-date source for security information is at CERT (6). Server protection is becoming automatic, in the sense of being invisible to the user, as network software acquires built-in protection capabilities. Client attacks are best avoided by putting in place procedures controlling what can be downloaded, visiting only trusted Web sites, and using Internet-virus detection software. Client protection is a weak point, however, since it is difficult to control the apparently innocuous actions of users who might inadvertently introduce viruses,

Information can be intercepted in transit (on the Internet) and used for industrial intelligence purposes: Generally speaking, clinical trial data are of low intrinsic value compared to financial data, and methods to protect them in transit need not be as complex and expensive as those utilized in electronic commerce. The Secure Sockets Layer (SSL) technology incorporated in many Web servers and browsers is quite up to handling this problem for clinical trials, and

Information can be intercepted in transit (on the Internet) and corrupted or falsified, and unauthorized persons can gain access to entering, updating, or viewing the information on a Web site via a browser: These general areas continue to receive a great deal of attention and there are many different tools commercially available to address them. These areas also present substantial conceptual problems for the nonspecialist as there is a lack of standards, and solutions tend to be targeted to particular business problems and equipment configurations. These areas can be characterized in the following ways (7):

Confidentiality: Verifying that information is accessed (read or written) only by a specific set of recipients or originators, Authentication: Identifying an individual or computer to ensure that he/it is a member of a specific set, complementary to `Confidentiality,'

Nonrepudiation: Ensuring that people cannot deny their electronic actions,

Replay prevention: Ensuring that transactions cannot be repeated,

Integrity: Verifying that information received is what was put there by the originator,

Access control: Verifying that resources are under the exclusive control of authorized parties, and ensuring that unauthorized persons are denied access, and

Availability: Ensuring that data and server resources are up and running when needed, and determining whether any downtime was caused by security-related incidents.

The Secure Virtual Private Network (SVPN) is a technology that, utilizing cryptographic techniques, creates secure

Internet communications between computers (including mobile users) and their network servers as if they were connected directly to the home network. SVPNs appear to accommodate many of the requirements discussed here in a reasonably simple and inexpensive way. At the present time, however, there are several obstacles to their adoption. One is that standards for SVPNs are not set, leading to interoperability problems reminiscent of those encountered with incompatible browsers, and another is that there may be conditions that the participants in a SVPN must satisfy. For example, a user's intervening firewall could interfere with use of SVPNs, and some SVPNs require specific operating systems on servers and client computers. Another problem is that SVPNs may introduce considerable delays in communications, resulting in the frustration of users and consequent lack of acceptance. This technology is changing rapidly and interoperability problems are becoming less substantial.

Intrusion detection and response systems capable of detecting intruders and automatically terminating the connection are beginning to appear on the market. The combination of SVPNs and intrusion detection technologies may offer a comprehensive solution as these technologies mature, but its widespread impact within an organization requires commitment from management for successful implementation.

Security is a rapidly changing part of Internet infrastructure and such emerging consumer technologies as smart cards, which are a product of the credit card industry, may have a significant impact. Within a few years the convergence of standardized smart card readers on computers, for identification, and simple to use SVPNs could very well be sufficient for the security needs of clinical trials.

ESTABLISHING DIRECTIONS

The new modality of the Web provides the opportunity for new ways of solving problems, and new opportunities for achieving business goals. Of course, no matter how attractive a technology might appear, the various participants in **clinical trials** will view it in their own terms. Utilization of the **Internet** in the **conduct** of clinical trials should be viewed within an overall information systems framework, but not as a monolithic task. The first step is to clarify strategic goals by looking at the ways in which clinical trials will be conducted and how this relates to the connectivity, communication, and security issues already discussed. Strategic goals, and the tactics to realize them, will differ among participants.

An international pharmaceutical company may have a proprietary network and a large technical staff, while a CRO may have to deal with the requirements of many sponsors concurrently. In any case, it will be necessary to identify the basic tasks and to set priorities for addressing them. It is especially important to clarify the `Internet roles' of the various participants since a lack of attention to this can lead to overcomplication, underachievement of goals, and mission failure. Some of the considerations to be addressed are:

What is the degree of persistency of the participants? There might be long term relationships to be supported, such as between a sponsor or CRO and a Phase I clinic, between a sponsor and a CRO in a preferred provider relationship, or between the sites and the central office of a site management organization. In many cases, there will short-term arrangements between a sponsor or CRO and trial sites. Short-term arrangements can require training, provisioning, and support that inhibit the use of Web-based solutions. Benefits can accrue even in short-term relationships through use of the Web for distributing reports rather than acquiring data,

Are patient data (case report forms) to be collected via the Internet? If this is considered to be source data, then there must be a high degree of attention paid to its integrity,

Are logistical data, such as enrollment and patient progress, clinical trial material consumption and restocking, financial memos, and so forth, to be handled? This kind of activity is substantially easier to implement than that of acquiring patient data, and has a high value in trial management, and

Are trial communications, such as data clarifications, monitor/coordinator e-mails, procedure clarifications, and so forth, to be handled? What is the value attached to storing all of these communications in the project database, in contrast to using conventional e-mail that may distribute communications and make a comprehensive view difficult to obtain?

Use of the Web has the potential for better cost control and more realistic budgeting due to the ease of obtaining pertinent information in a timely manner. There are considerable technical hurdles to overcome, among these being that building robust Web-based applications calls for extensive design and highly competent programmers. There have been many instances, in clinical trials and other businesses, where difficulty and resource requirements have been understated, leading to wasted time and money, and failed projects. Nevertheless, this technological opportunity, realistically handled, can lead to significant benefits.

In any case, Moore's Law, that computing power doubles every 18-24 months while price remains constant, continues to hold and today's good solution may be inefficient tomorrow. Conversely, what appears out of reach today may be commonplace tomorrow. It is possible to deal with this high rate of technological change if the underlying business needs are explicitly stated and understood, and the advantages to participants are stated in business terms.

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Informed consent for clinical trials: A comparative study of standard versus simplified forms

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Abstract:
A study was conducted to test the hypothesis that a simplified informed consent form would be less intimidating and more easily understood by individuals with low-to-marginal reading skills. Findings raise serious questions regarding the adequacy of the design of written informed consent documents for the substantial proportion of Americans with low-to-marginal literacy skills.

Full Text:

[Headnote]

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[Headnote]

Background: A high level of reading skill and comprehension is necessary to understand and complete most consent forms that are required for participation in clinical research studies. This study was conducted to test the hypothesis that a simplified consent form would be less intimidating and more easily understood by individuals with low-to-marginal reading skills. Methods: During July 1996, 183 adults (53 patients with cancer or another medical condition and 130 apparently healthy participants) were tested for reading ability and then asked to read either the standard Southwestern Oncology Group (SWOG) consent form (16th grade level) or a simplified form (7th grade level) developed at Louisiana State University Medical Center-Shreveport (LSU). Participants were interviewed to assess their attitudes toward and comprehension of the form read. Then they were given the alternate consent form and asked which one they preferred and why. Results: Overall, participants preferred the LSU form (62%; 95% confidence interval [CI] = 54.8%69.2%) over the SWOG form (38%; 95% CI = 30.8%45.2%) (P = .0033). Nearly all participants thought that the LSU form was easier to read (97%; 95% CI = 93.1%99.9%) than the SWOG form (75%; 95% CI = 65.1%85.7%) (P<.0001). However, the degree to which the participants understood the forms was essentially the same for the LSU form (58%; 95% CI = 48.6%-67.0%) and the SWOG form (56%; 95% CI = 43.8%lo-66.8%). Implications: These findings raise serious questions regarding the adequacy of the design of written informed consent

documents for the substantial proportion of Americans with low-to-marginal literacy skills. [J Natl Cancer Inst 1998;90:668-74]

Clinicians and researchers must **obtain** informed **consent** from patients before enrolling them in **clinical trials**. To ensure that patients fully understand factors related to their care, the Food and Drug Administration (FDA) requires that consent documents contain detailed information regarding eight basic elements of informed consent (1). However, little attention has been given to how well patients comprehend these elements (2-10) despite the fact that health care providers have an ethical and legal responsibility to ensure that patients understand their participation in research (7).

Standard consent forms are written at too difficult a level for many patients to read and comprehend, especially those with low literacy skills (5,8,9-20). The National Adult Literacy Survey (21) found that 21% of U.S. adults are functionally illiterate, and an additional 27% have marginal literacy skills. These figures indicate that a substantial proportion of patients may not be able to read and understand the consent forms that are currently used in clinical research (11,12,18). Despite recommendations that forms be simplified to a 6th-8th grade level, most forms continue to be written at or above a 12th grade level (5,8,1012,14-20,22,23,24).

Factors associated with decreased comprehension of informed consent include limited education, increasing age of the patient, and the readability of the consent form (2,6,8,12). Results are mixed regarding the effect of simplified patient education material and consent forms on patient comprehension (25). Lowering the readability level alone seems to have little impact (2,8). However, researchers in the field of patient education have found that the appeal and comprehension of health education material can be increased by improving the presentation through use of instructional graphics, headers, and questions, as well as use of bold text and colors (12,18,25-31). To our knowledge, the effect of improving the presentation of consent forms on comprehension has not been previously tested.

The National Cancer Institute has called for research aimed at simplifying the informed consent process, at improving comprehension, and at identifying methods to provide specific study information to diverse populations in cancer prevention and treatment trials (7). The purpose of this study was to test the hypothesis that a simplified consent form, written at a lower reading level and developed with input from patients, would improve the comprehension and attitude of participants toward the form.

Subjects and Methods

During July 1996, 183 adults recruited from private and university oncology clinics and a low-income housing complex were tested for reading ability and given either a standard Southwestern Oncology Group (SWOG) consent form for a phase III breast cancer clinical trial or a simplified booklet-style form developed at Louisiana State University Medical Center- Shreveport (LSU). Patients were interviewed using an oral questionnaire that assessed attitudes and comprehension of the consent form they were given. Upon completion of the interview, the patients were given time to review the alternate consent form and were asked additional questions as to which they preferred, why, and whether they would prefer to receive both forms. They were also asked to rate each consent form quantitatively by placing a vertical mark on a Likert-scale (16-cm horizontal line that was labeled "bad" at 0 cm and "good" at 16 cm).

Either the SWOG or the LSU form was presented first on alternate days. The entire interview was completed in about 25 minutes using the SWOG form or 10-12 minutes using the LSU form. Since each interview took twice as long on the day that the SWOG form was initially given, fewer people were tested in the allotted time. Sixty-nine adults were initially given the SWOG form, and 114 were initially given the LSU form. Because the study only involved assessing patient attitudes and comprehension, it received an exemption from the Institutional Review Board at LSU.

Patient Population

Of the 205 adults who were approached and asked to participate in the study, 22 refused. The reasons given for refusal were as follows: Eight patients did not want to participate, six could not see well, four could not read, and four were tired or felt ill.

Of the 183 adults tested, 18 (10%) were tested at a private oncology clinic in Shreveport, 28 (15%) at a low-income housing complex in Shreveport, and 137 (75%) at the LSU Hematology/Oncology Clinic (see Table 1). At the private and university clinics, patients or accompanying friends or family members were approached in the clinic waiting rooms. If they agreed to participate, they were taken to a private room and tested. Residents of a

housing complex near LSU were recruited by the president of the residents' council and asked to participate in a study to elicit input on consent forms used at LSU. These participants met at one of two sessions held at a community center where they were invited into a private room for testing. At the first session, 14 participating residents were initially given the SWOG form. At the second session, 14 participating residents were initially given the LSU form. While equal numbers of participants at the housing complex were tested with each form, the duration of testing when the SWOG form was supplied first was approximately double that when the LSU form was supplied first. The residents' council was paid a stipend of $300.

Study Instruments

The Rapid Estimate of Adult Literacy in Medicine (REALM) (32) is an individually administered reading recognition test designed for use in medical settings. Reading recognition tests do not indicate the readers' comprehension, only their ability to read aloud words in isolation (33). Reading recognition scores are accepted as useful predictors of general reading ability and are an indicator of functional literacy skills (33,34). The REALM is highly correlated with other standardized tests of reading recognition (15,16,18) as well as the Test of Functional Health Literacy in Adults (11,35). The raw scores range from 0 to 66 and can be converted into four reading grade levels: 3rd grade and below (scores of 0-18), 4th-6th grades (scores of 1944), 7th-8th grades (scores of 45-60), and 9th grade and above (scores of 61-66). The REALM can be administered and scored in 2-3 minutes by personnel with minimal training.

A structured oral questionnaire was developed by the investigators. This questionnaire was pilot-tested over a period of 2 weeks at the LSU Hematology/ Oncology Clinic to ensure that the questions were clear and understandable to patients. The final version of the questionnaire-the one used in this studyassessed patient demographics and contained 22 attitude and comprehension questions.

Description of the Consent Forms

The standard research consent form used in this study is the one developed by SWOG for protocol #8851. It is entitled, "Phase III Comparison of Combination Chemotherapy (CAF) & Chemohormonal Therapy (CAF + Zoladex or CAF + Zoladex and Tamoxifen) in Premenopausal Women with Axillary-Node Positive, Receptor-Positive Breast Cancer, Intergroup" (see "Appendix" section). The SWOG consent form is a seven-page, single-spaced document that contains 3438 words. The average sentence length is 21 words, and the form has no graphics. The readability of the SWOG form was calculated using Grammatik IV software (Reference Software International, San Francisco) (36), which revealed a Flesch-Kincaid index (37) at the 12th grade reading level and a Fog index (38) at the 16th grade level.

The LSU form was designed with input from patients. Individual patient interviews in the LSU Hematology/Oncology clinic elicited information on appeal, reading ease, and comprehension. No patient who assisted with the development of the LSU consent form or the questionnaire participated in the main study. Based on patient feedback, the form was revised two times before the study was initiated. The readability of the LSU form, calculated using Grammatik IV software, was at the 5th grade level on the Flesch-Kincaid index and at the 7th grade level on the Fog index. It was formatted as a seven-page booklet containing 524 words. The title, "Breast Cancer, You Can Help Your Doctors Find Better Treatments," appeared on the front cover with a seal of "LSU Medical Center Shreveport." The text had an average sentence length of 12.5 words, used colored headers, had ample white space, and included 11 culturally sensitive instructional graphics (Fig. 1).

Analysis of Data

A chi-squared test was used to determine the differences in attitude and comprehension between the two forms, as well as to compare education and reading levels between the two study groups. The Kruskal-Wallis one-way analysis of variance was used to compare the participants' comprehension of forms across reading levels. The Mann-Whitney rank-sum test and the Wilcoxon signed-rank test were used to determine differences in patient preference between the SWOG and LSU forms. All P-values were derived from two-sided tests; 95% confidence intervals (CIs) were determined for all points estimates.

Results

Of the 183 adults interviewed, 102 (56%) were African American, 81 (44%) were white, and 139 (76%) were female (Table 1). The median age of the participants was 48 years (range, 19-85 years). Fifty-three (29%) of the adults tested had cancer, but none were candidates for participation in the clinical trial for which the consent forms were prepared. Patients had completed an average of 11.9 years in school. The mean raw score on the REALM was 52, which indicates that the patients were reading, on average, at a 7th-8th grade level. Forty-six (25%)

scored below 45, which indicates that they were reading on a 6th grade level or below and that they could be considered marginally literate. Education levels and reading raw scores were slightly higher in the group that was initially given the SWOG form but did not differ significantly from the group initially given the LSU form (Table 1).

Overall, participants preferred the LSU form (62%; 95% CI = 54.8%-69.2%) over the SWOG form (38%; 95% CI = 30.8%-45.2%) (P = .0033). Nearly all participants thought the LSU form was easy to read (97%; 95% CI = 93.1%99.9%) in contrast to the SWOG form (75%; 95% CI = 65.1%-85.7%) (P<.0001). Participants reported they felt less comfortable with the SWOG form (20%; 95% CI = 10.6%-30.0%) compared with the LSU form (6%; 95% CI = 1.6%-10.6%) (P = .0099). They were more frequently frightened by the SWOG form (30%; 95% CI = 19.3%-41.5%) than the LSU form (13%; 95% CI = 6.9%-19.5%) (P = .0079). They thought that the SWOG form was more likely than the LSU form to discourage them from participating in the breast cancer clinical trial (12% [95% CI = 3.9%-19.3%] versus 2% [95% CI = 0%-4.3%] respectively; P = .0135) (Fig. 2). Very few participants were insulted by either form: Only 2% given the SWOG form first and 1% of those given the LSU form first indicated that they were insulted. A majority of the participants reported that they would read the entire form if given to them by a physician (86% SWOG form [95% CI = 77.0%-94.0%] versus 90% LSU form [95% CI = 84.9%-95.9%]). While 75% (95% CI = 69.0%-81.8%) of the participants thought the form that they had read contained the right amount of information, 17% (95% CI = 8.3%-26.5%) initially given the SWOG form thought it contained too much information, and 22% (95% CI = 14.2%-29.6%) initially given the LSU form felt it contained too little information.

On the Likert scale, the LSU form was rated significantly better (11.8; standard deviation [SD] = 4.1) than the SWOG form (10.2; SD = 3.5) (P<.0001). While participants tended to prefer the consent form they were first asked to read, those first given the LSU form preferred it to a greater degree than those first given the SWOG form. Among adults who read below a 9th grade level, the majority preferred the LSU form even when they were given the SWOG form first; 46% (95% CI = 34.0%58.0%) of those first given the SWOG form preferred it, and 79% (95% CI = 71.4%-86.6%) of those first given the LSU form preferred that form.

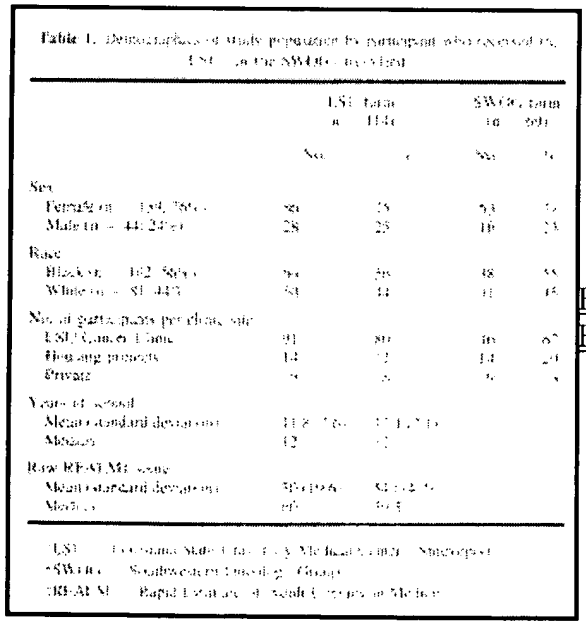

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Table 1.

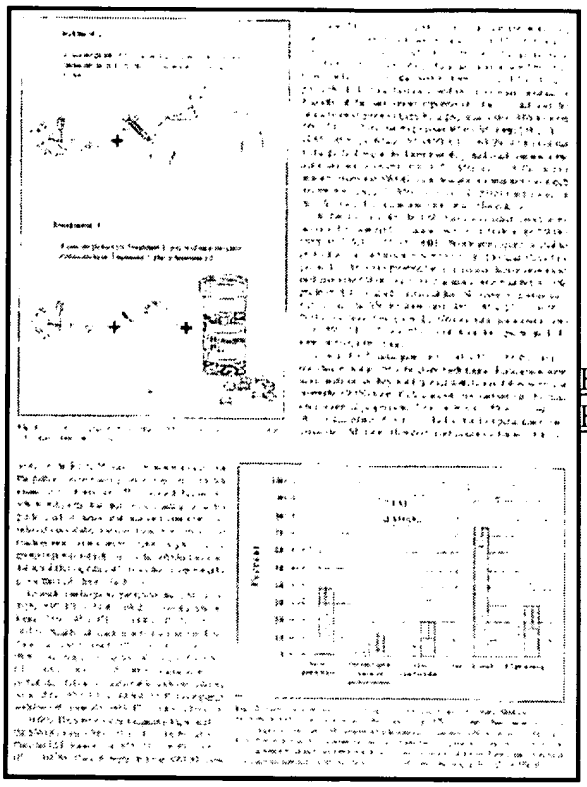

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Fig. 1. Fig. 2.

A total of 115 participants (63%; 95% CI = 55.9%-70.1%) said they would prefer to be given both forms. Participants were more likely to say they would prefer both forms if they were first given the SWOG form. Preference of form did not vary by race, since identical proportions (59%) of black (95% CI = 49.3%68.7%) and white (95% CI = 48.1%-69.9%) participants preferred the LSU form. However, participant preference did vary by reading and education level: Those with lower literacy levels preferred the simplified LSU form. Participants reading at an 8th grade level and below preferred the LSU over the SWOG form (70% [95% CI = 61.8%-79.2%] versus 30% [95% CI = 21.8%-39.2%]). Those reading at a 9th grade level or above also preferred the LSU form but to a lesser extent (52% [95% CI = 41.1%-62.9%] versus 48% [95% CI = 37.1%-58.9%]).

Overall, participant comprehension was the same for both forms-58% for the LSU form (95% CI = 48.6%-67.0%) and 56% for the SWOG form (95% CI = 43.8%-66.8%)-with no significant differences on any of the 10 individual questions used to assess this. The participants' scores on the comprehension questions were related to their reading ability. Participants reading at or below a 3rd grade level had an average comprehension score of 21% (95% CI = 1.3%-40.7%), those reading at a 4th-6th grade level averaged 39% (95% CI = 20.6%57.4%), those at a 7th-8th grade level scored 54% (95% CI = 40.4%-67.6%), while those reading at or above a 9th grade level scored 72% (95% CI = 62.2%-81.8%) (P = .038 for trend). Adults reading at or above a 9th grade level had significantly higher comprehension of both the SWOG form (71%; 95% CI = 61.1%-80.9%) and the LSU form (73%; 95% CI = 63.3%82.7%) than those reading on or below an 8th grade level (SWOG form, 43% [95% CI = 33.0%-53.0%] versus LSU form, 45% [95% CI=35.0%-55.0%]; P<.0001).

Results of the 10 comprehension questions are shown in Table 2. Of note, the participants' comprehension of basic treatment information was very low. For example, less than a third of the participants tested understood the differences in the three treatments for the breast cancer protocol (14% [95% CI = 5.7%-22.3%] for the SWOG form versus 25% [95% CI = 16.9%-33.1%] for the LSU form) or what determines which treatment you get (23% [95% CI = 12.9%-33.1%] for the SWOG form versus 18% [95% CI = 10.8%-25.2%] for the LSU form).

Discussion

Informed consent is an interactive, multifaceted process, of which one important element is the informed consent document. In clinical research, participants must be given informed consent documents that they can understand (6,7,28), yet participants in this study comprehended just over half of the information in the standard SWOG consent form (56%) or in the simplified LSU form (58%). Making the form more suitable by using suggestions from the literature (12,16,18,24-30) and eliciting participant input made the consent document easier to read and less frightening to the participants but did not improve comprehension of the elements contained within it.

The results of this study confirm those of previous studies that showed comprehension of informed consent documents poses problems for many participants. Williams et al. (11) found that fewer than half of participants in public hospitals in Atlanta and Los Angeles could comprehend the standard consent document used for invasive procedures at the Atlanta hospital. Cassileth et al. (24) found that 60% of patients participating in a study conducted in Philadelphia understood the purpose and nature of medical procedures to which they had signed written consent just 1 day before and that only 40% of the participants reported they had read the form carefully. Cassileth et al. (24) concluded that the difficulty of the material and its legalistic wording imposed barriers to the patients' comprehension of information intended to facilitate informed decisions.

To improve comprehension, consent forms should be brief and direct. They should avoid legal jargon and should be written at appropriate reading levels using plain English (12,19). Following these recommendations and those in the participant education literature, we developed a more suitable form written on a 7th grade level. This form was rated as being easier to read than the SWOG form (16th grade level) by the participants in the study, yet their comprehension of the content was not improved. These findings support the results of another study (2), which showed that simplifying informed consent materials alone does not significantly improve participant comprehension. On the other hand, Young et al. (8) reported significantly (P<.OS) higher participant comprehension using a simplified form (6th grade level) compared with a standard form (16th grade level). While the differences reported by Young et al. reached statistical significance, they seem to be of marginal clinical importance: They found a mean difference of only 0.6 more questions (of the 21 questions) answered correctly on the "low reading level consent form." Research is lacking as to the methods by which participant comprehension of informed consent documents can be increased to a clinically acceptable level or even what a clinically acceptable level might be.

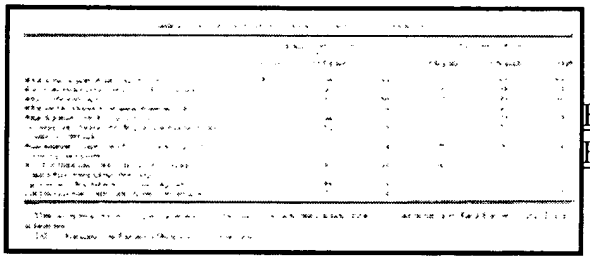

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Table 2.

Our previous research (11,18,25), as well as other research, indicated that participants with very low literacy would probably not be able to adequately comprehend either standard or simplified consent form. Williams et al. (11) suggested that simplifying the text to an approximately 6th grade level might allow marginally literate participants to comprehend the documents. We hypothesized that a form written on a 7th grade level would be better understood by participants with both adequate and marginal literacy levels in comparison to a standard form written on a 16th grade level. We further hypothesized that those who would benefit most from the simplified form would be participants with marginal literacy skills. In actuality, participants with adequate literacy levels (i.e., those reading at or above a 9th grade level) comprehended both forms at marginally adequate levels: 73% the simplified LSU form and 71% the standard SWOG form. Participants with marginal literacy skills (i.e., those reading at a 7th-8th grade level) understood approximately half of the information on either form. Although comprehension was higher with the simplified form, the difference was not statistically significant.

Participants with inadequate literacy skills understood only a minimal amount of the content of either form. Those reading at a 4th-6th grade level comprehended 41% of the LSU form and 35% of the SWOG form. The 17 participants with the lowest literacy, (0-3rd grade reading level), who could be considered functionally illiterate, comprehended only 20% of the LSU form and 10% of the SWOG form. These findings indicate that 1) standard forms do not adequately inform participants (particularly those with marginal and inadequate literacy skills) and 2) simplified forms, when used alone, do not significantly improve the comprehension of participants-at any reading level.

Given that approximately 90 million adults in the United States have inadequate literacy skills (21), our findings raise ethical and legal questions about the ability of informed consent documents to aid all individuals in the decision-making process for study participation. These adults may not be able to read and understand the forms they are signing, and they may not let clinicians or researchers know their problem since most participants who have reading difficulties are embarrassed to admit it (39). Clinicians should also be aware that patients with inadequate literacy skills may be anxious about being expected to read and sign documents and to communicate with physicians (18,34,39). Patients with low literacy may also have problems with basic physician/participant

communication. Recent studies (40,41) have shown that participants with extremely limited literacy skills may have limited health knowledge and may not understand basic health concepts such as the purpose of a mammogram. Such individuals often do not understand what the physician has said and may not be willing to ask physicians for clarification of information (18,39).

In an attempt to sufficiently inform patients so they can make a rational decision about participating in a research study, the Department of Health and Human Services (1) developed detailed regulations concerning the minimum information that consent forms should contain. Subsequently, consent forms have expanded in length (19,23). However, in our study and in other studies, consent forms that are longer and more detailed did not improve the readability of the form or its comprehension by participants (19,23). In this study, participants preferred the shorter, easy-to-read material and found it less frightening. Perhaps long forms written on a college level, though intended to provide complete information for informed consent of a clinical trial, may inadvertently be frightening and overwhelming, especially for low-level readers.

In our study, even those participants who read on at least a 9th grade level were not offended by the simple form. Only seven of 183 participants reported that they were insulted by either form, and none were offended by the simplicity of the LSU form. This observation supports earlier findings (25,26) that neither highly literate nor high-income participants are offended by simple material.

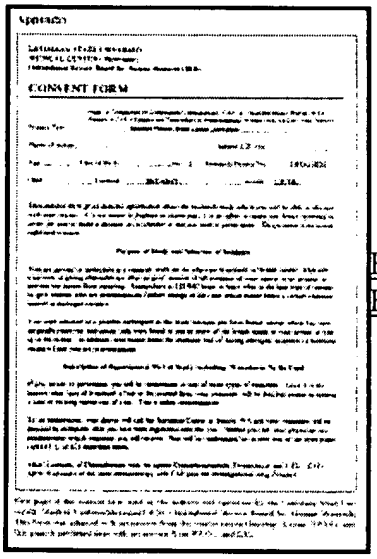
Ethicists and patient educators (8,17,24,42-46) are recommending that patients be included in the development of patient education materials and forms to ensure that the materials include information important to them and are more understandable, appealing, and culturally sensitive. Reid et al. (45) found that patients and physicians differed in what they thought was important to include in written material. This may also be true for informed consent. Turner et al. (46) found that physicians did not identify the outcomes that were most important to cancer patients. For example, patients indicated that acute side effects were as important as long-term side effects. Side effects that were not routinely emphasized, such as energy loss or change in appearance, were more important to patients. Cassileth et al. (24) found that 80% of participants viewed consent forms as a protection for physicians.

In developing the LSU simplified consent form we elicited individual patient feedback on various versions of the form and we modified it over a 2-week period based on this input. While patients liked the information presented in booklet form, they felt it was important for a consent form to look official and they requested a formal cover page and legally detailed signature page. A one-page insert was added as a supplement to the booklet.

There are several limitations to this study. First, although the different consent forms were administered on alternate days, the study was not randomized in the traditional sense. More participants were initially given the LSU form because more questionnaires could be completed in each testing period when the shorter, simplified LSU form was reviewed by participants first. Second, none of the participants were candidates for the phase III breast cancer trial for which the consent form was designed. Therefore, neither the SWOG nor the LSU consent form was specifically relevant to them, and none of the participants were dealing with an actual recent diagnosis of cancer. They did not have to truly consider participation in a clinical trial and, as such, did not have associated anxiety that might interfere with comprehension of both verbal and written communication. Third, in a standard clinical encounter, a written informed consent document is supplemental to an interactive, "face-to-face" consent process. The design of our study did not include this active continuing process. Comprehension was limited to what the participant could understand from reading the document.

Another potential problem is that, although the questionnaire was pilot-tested for comprehension, the validity of the questionnaire was not extensively tested to determine the appropriateness of the questions. In addition, the questions did not assess the participants' comprehension of all eight essential elements of informed consent as outlined by the FDA. The Deaconess Informed Consent Comprehension Test (3), published after this study was conducted, provides 14 questions that could be used to assess all eight elements of informed consent. The design of the study also does not control for previous knowledge and does not distinguish between recall and true comprehension. However, there is no published standard that defines a coherent methodology to test comprehension in a similar setting.

In conclusion, our findings indicate that simplifying informed consent material alone makes the forms more appealing and easier to read but will not improve comprehension. Research is needed to determine the methods to increase comprehension, especially for participants with inadequate or marginal reading skills. Input from participants and recognition of hidden illiteracy will be critical in the development of better informed consent.



CONSENT FORM

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Appendix

[Footnote]
Note
Manuscript received July 21, 1997; revised February 13, 1998: accepted March 5, 1998.

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Informed consent for clinical trials: A comparative study of standard versus simplified forms

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Forms

Abstract:
A study was conducted to test the hypothesis that a simplified informed consent form would be less intimidating and more easily understood by individuals with low-to-marginal reading skills. Findings raise serious questions regarding the adequacy of the design of written informed consent documents for the substantial proportion of Americans with low-to-marginal literacy skills.

Full Text:

[Headnote]
Terry C. Davis, Randall F. Holcombe, Hans J. Berkel, Sumona Pramanik Stephen G. Divers*

[Headnote]
Background: A high level of reading skill and comprehension is necessary to understand and complete most consent forms that are required for participation in clinical research studies. This study was conducted to test the hypothesis that a simplified consent form would be less intimidating and more easily understood by individuals with low-to-marginal reading skills. Methods: During July 1996, 183 adults (53 patients with cancer or another medical condition and 130 apparently healthy participants) were tested for reading ability and then asked to read either the standard Southwestern Oncology Group (SWOG) consent form (16th grade level) or a simplified form (7th grade level) developed at Louisiana State University Medical Center-Shreveport (LSU). Participants were interviewed to assess their attitudes toward and comprehension of the form read. Then they were given the alternate consent form and asked which one they preferred and why. Results: Overall, participants preferred the LSU form (62%; 95% confidence interval [CI] = 54.8%69.2%) over the SWOG form (38%; 95% CI = 30.8%45.2%) (P = .0033). Nearly all participants thought that the LSU form was easier to read (97%; 95% CI = 93.1%99.9%) than the SWOG form (75%; 95% CI = 65.1%85.7%) (P<.0001). However, the degree to which the participants understood the forms was essentially the same for the LSU form (58%; 95% CI = 48.6%-67.0%) and the SWOG form (56%; 95% CI = 43.8%lo-66.8%). Implications: These findings raise serious questions regarding the adequacy of the design of written informed consent

documents for the substantial proportion of Americans with low-to-marginal literacy skills. [J Natl Cancer Inst 1998;90:668-74]

Clinicians and researchers must **obtain** informed **consent** from patients before enrolling them in **clinical trials**. To ensure that patients fully understand factors related to their care, the Food and Drug Administration (FDA) requires that consent documents contain detailed information regarding eight basic elements of informed consent (1). However, little attention has been given to how well patients comprehend these elements (2-10) despite the fact that health care providers have an ethical and legal responsibility to ensure that patients understand their participation in research (7).

Standard consent forms are written at too difficult a level for many patients to read and comprehend, especially those with low literacy skills (5,8,9-20). The National Adult Literacy Survey (21) found that 21% of U.S. adults are functionally illiterate, and an additional 27% have marginal literacy skills. These figures indicate that a substantial proportion of patients may not be able to read and understand the consent forms that are currently used in clinical research (11,12,18). Despite recommendations that forms be simplified to a 6th-8th grade level, most forms continue to be written at or above a 12th grade level (5,8,1012,14-20,22,23,24).

Factors associated with decreased comprehension of informed consent include limited education, increasing age of the patient, and the readability of the consent form (2,6,8,12). Results are mixed regarding the effect of simplified patient education material and consent forms on patient comprehension (25). Lowering the readability level alone seems to have little impact (2,8). However, researchers in the field of patient education have found that the appeal and comprehension of health education material can be increased by improving the presentation through use of instructional graphics, headers, and questions, as well as use of bold text and colors (12,18,25-31). To our knowledge, the effect of improving the presentation of consent forms on comprehension has not been previously tested.

The National Cancer Institute has called for research aimed at simplifying the informed consent process, at improving comprehension, and at identifying methods to provide specific study information to diverse populations in cancer prevention and treatment trials (7). The purpose of this study was to test the hypothesis that a simplified consent form, written at a lower reading level and developed with input from patients, would improve the comprehension and attitude of participants toward the form.

Subjects and Methods

During July 1996, 183 adults recruited from private and university oncology clinics and a low-income housing complex were tested for reading ability and given either a standard Southwestern Oncology Group (SWOG) consent form for a phase III breast cancer clinical trial or a simplified booklet-style form developed at Louisiana State University Medical Center- Shreveport (LSU). Patients were interviewed using an oral questionnaire that assessed attitudes and comprehension of the consent form they were given. Upon completion of the interview, the patients were given time to review the alternate consent form and were asked additional questions as to which they preferred, why, and whether they would prefer to receive both forms. They were also asked to rate each consent form quantitatively by placing a vertical mark on a Likert-scale (16-cm horizontal line that was labeled "bad" at 0 cm and "good" at 16 cm).

Either the SWOG or the LSU form was presented first on alternate days. The entire interview was completed in about 25 minutes using the SWOG form or 10-12 minutes using the LSU form. Since each interview took twice as long on the day that the SWOG form was initially given, fewer people were tested in the allotted time. Sixty-nine adults were initially given the SWOG form, and 114 were initially given the LSU form. Because the study only involved assessing patient attitudes and comprehension, it received an exemption from the Institutional Review Board at LSU.

Patient Population

Of the 205 adults who were approached and asked to participate in the study, 22 refused. The reasons given for refusal were as follows: Eight patients did not want to participate, six could not see well, four could not read, and four were tired or felt ill.

Of the 183 adults tested, 18 (10%) were tested at a private oncology clinic in Shreveport, 28 (15%) at a low-income housing complex in Shreveport, and 137 (75%) at the LSU Hematology/Oncology Clinic (see Table 1). At the private and university clinics, patients or accompanying friends or family members were approached in the clinic waiting rooms. If they agreed to participate, they were taken to a private room and tested. Residents of a

housing complex near LSU were recruited by the president of the residents' council and asked to participate in a study to elicit input on consent forms used at LSU. These participants met at one of two sessions held at a community center where they were invited into a private room for testing. At the first session, 14 participating residents were initially given the SWOG form. At the second session, 14 participating residents were initially given the LSU form. While equal numbers of participants at the housing complex were tested with each form, the duration of testing when the SWOG form was supplied first was approximately double that when the LSU form was supplied first. The residents' council was paid a stipend of $300.

Study Instruments

The Rapid Estimate of Adult Literacy in Medicine (REALM) (32) is an individually administered reading recognition test designed for use in medical settings. Reading recognition tests do not indicate the readers' comprehension, only their ability to read aloud words in isolation (33). Reading recognition scores are accepted as useful predictors of general reading ability and are an indicator of functional literacy skills (33,34). The REALM is highly correlated with other standardized tests of reading recognition (15,16,18) as well as the Test of Functional Health Literacy in Adults (11,35). The raw scores range from 0 to 66 and can be converted into four reading grade levels: 3rd grade and below (scores of 0-18), 4th-6th grades (scores of 1944), 7th-8th grades (scores of 45-60), and 9th grade and above (scores of 61-66). The REALM can be administered and scored in 2-3 minutes by personnel with minimal training.

A structured oral questionnaire was developed by the investigators. This questionnaire was pilot-tested over a period of 2 weeks at the LSU Hematology/ Oncology Clinic to ensure that the questions were clear and understandable to patients. The final version of the questionnaire-the one used in this studyassessed patient demographics and contained 22 attitude and comprehension questions.

Description of the Consent Forms

The standard research consent form used in this study is the one developed by SWOG for protocol #8851. It is entitled, "Phase III Comparison of Combination Chemotherapy (CAF) & Chemohormonal Therapy (CAF + Zoladex or CAF + Zoladex and Tamoxifen) in Premenopausal Women with Axillary-Node Positive, Receptor-Positive Breast Cancer, Intergroup" (see "Appendix" section). The SWOG consent form is a seven-page, single-spaced document that contains 3438 words. The average sentence length is 21 words, and the form has no graphics. The readability of the SWOG form was calculated using Grammatik IV software (Reference Software International, San Francisco) (36), which revealed a Flesch-Kincaid index (37) at the 12th grade reading level and a Fog index (38) at the 16th grade level.

The LSU form was designed with input from patients. Individual patient interviews in the LSU Hematology/Oncology clinic elicited information on appeal, reading ease, and comprehension. No patient who assisted with the development of the LSU consent form or the questionnaire participated in the main study. Based on patient feedback, the form was revised two times before the study was initiated. The readability of the LSU form, calculated using Grammatik IV software, was at the 5th grade level on the Flesch-Kincaid index and at the 7th grade level on the Fog index. It was formatted as a seven-page booklet containing 524 words. The title, "Breast Cancer, You Can Help Your Doctors Find Better Treatments," appeared on the front cover with a seal of "LSU Medical Center Shreveport." The text had an average sentence length of 12.5 words, used colored headers, had ample white space, and included 11 culturally sensitive instructional graphics (Fig. 1).

Analysis of Data

A chi-squared test was used to determine the differences in attitude and comprehension between the two forms, as well as to compare education and reading levels between the two study groups. The Kruskal-Wallis one-way analysis of variance was used to compare the participants' comprehension of forms across reading levels. The Mann-Whitney rank-sum test and the Wilcoxon signed-rank test were used to determine differences in patient preference between the SWOG and LSU forms. All P-values were derived from two-sided tests; 95% confidence intervals (CIs) were determined for all points estimates.

Results

Of the 183 adults interviewed, 102 (56%) were African American, 81 (44%) were white, and 139 (76%) were female (Table 1). The median age of the participants was 48 years (range, 19-85 years). Fifty-three (29%) of the adults tested had cancer, but none were candidates for participation in the clinical trial for which the consent forms were prepared. Patients had completed an average of 11.9 years in school. The mean raw score on the REALM was 52, which indicates that the patients were reading, on average, at a 7th-8th grade level. Forty-six (25%)

scored below 45, which indicates that they were reading on a 6th grade level or below and that they could be considered marginally literate. Education levels and reading raw scores were slightly higher in the group that was initially given the SWOG form but did not differ significantly from the group initially given the LSU form (Table 1).

Overall, participants preferred the LSU form (62%; 95% CI = 54.8%-69.2%) over the SWOG form (38%; 95% CI = 30.8%-45.2%) (P = .0033). Nearly all participants thought the LSU form was easy to read (97%; 95% CI = 93.1%99.9%) in contrast to the SWOG form (75%; 95% CI = 65.1%-85.7%) (P<.0001). Participants reported they felt less comfortable with the SWOG form (20%; 95% CI = 10.6%-30.0%) compared with the LSU form (6%; 95% CI = 1.6%-10.6%) (P = .0099). They were more frequently frightened by the SWOG form (30%; 95% CI = 19.3%-41.5%) than the LSU form (13%; 95% CI = 6.9%-19.5%) (P = .0079). They thought that the SWOG form was more likely than the LSU form to discourage them from participating in the breast cancer clinical trial (12% [95% CI = 3.9%-19.3%] versus 2% [95% CI = 0%-4.3%] respectively; P = .0135) (Fig. 2). Very few participants were insulted by either form: Only 2% given the SWOG form first and 1% of those given the LSU form first indicated that they were insulted. A majority of the participants reported that they would read the entire form if given to them by a physician (86% SWOG form [95% CI = 77.0%-94.0%] versus 90% LSU form [95% CI = 84.9%-95.9%]). While 75% (95% CI = 69.0%-81.8%) of the participants thought the form that they had read contained the right amount of information, 17% (95% CI = 8.3%-26.5%) initially given the SWOG form thought it contained too much information, and 22% (95% CI = 14.2%-29.6%) initially given the LSU form felt it contained too little information.

On the Likert scale, the LSU form was rated significantly better (11.8; standard deviation [SD] = 4.1) than the SWOG form (10.2; SD = 3.5) (P<.0001). While participants tended to prefer the consent form they were first asked to read, those first given the LSU form preferred it to a greater degree than those first given the SWOG form. Among adults who read below a 9th grade level, the majority preferred the LSU form even when they were given the SWOG form first; 46% (95% CI = 34.0%58.0%) of those first given the SWOG form preferred it, and 79% (95% CI = 71.4%-86.6%) of those first given the LSU form preferred that form.

Table 1. Demographics of study population by participant who received the LSU* or the SWOG† form first

	LSU form (n = 114)		SWOG form (n = 69)	
	No.	%	No.	%
Sex				
Female (n = 139; 76%)	86	75	53	77
Male (n = 44; 24%)	28	25	16	23
Race				
Black (n = 102; 56%)	64	56	38	55
White (n = 81; 44%)	50	44	31	45
No. of participants per clinic site				
LSU Cancer Clinic	91	80	46	67
Housing projects	14	12	14	20
Private	9	8	9	13
Years of school				
Mean (standard deviation)	11.8 (2.6)	12.1 (2.1)		
Median	12	12		
Raw REALM‡ score				
Mean (standard deviation)	50 (19.6)	54 (14.2)		
Median	60	59.5		

*LSU = Louisiana State University Medical Center—Shreveport
†SWOG = Southwestern Oncology Group
‡REALM = Rapid Estimate of Adult Literacy in Medicine

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Table 1.

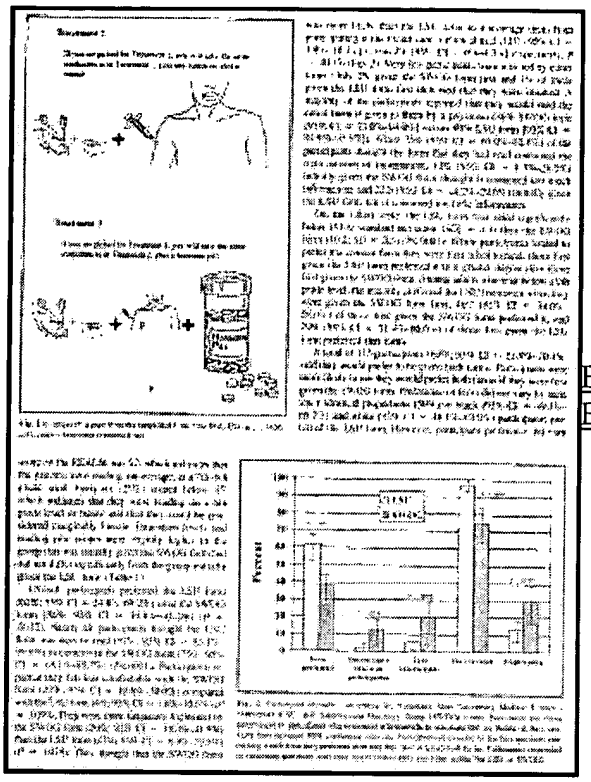

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Fig. 1. Fig. 2.

A total of 115 participants (63%; 95% CI = 55.9%-70.1%) said they would prefer to be given both forms. Participants were more likely to say they would prefer both forms if they were first given the SWOG form. Preference of form did not vary by race, since identical proportions (59%) of black (95% CI = 49.3%68.7%) and white (95% CI = 48.1%-69.9%) participants preferred the LSU form. However, participant preference did vary by reading and education level: Those with lower literacy levels preferred the simplified LSU form. Participants reading at an 8th grade level and below preferred the LSU over the SWOG form (70% [95% CI = 61.8%-79.2%] versus 30% [95% CI = 21.8%-39.2%]). Those reading at a 9th grade level or above also preferred the LSU form but to a lesser extent (52% [95% CI = 41.1%-62.9%] versus 48% [95% CI = 37.1%-58.9%]).

Overall, participant comprehension was the same for both forms-58% for the LSU form (95% CI = 48.6%-67.0%) and 56% for the SWOG form (95% CI = 43.8%-66.8%)-with no significant differences on any of the 10 individual questions used to assess this. The participants' scores on the comprehension questions were related to their reading ability. Participants reading at or below a 3rd grade level had an average comprehension score of 21% (95% CI = 1.3%-40.7%), those reading at a 4th-6th grade level averaged 39% (95% CI = 20.6%57.4%), those at a 7th-8th grade level scored 54% (95% CI = 40.4%-67.6%), while those reading at or above a 9th grade level scored 72% (95% CI = 62.2%-81.8%) (P = .038 for trend). Adults reading at or above a 9th grade level had significantly higher comprehension of both the SWOG form (71%; 95% CI = 61.1%-80.9%) and the LSU form (73%; 95% CI = 63.3%82.7%) than those reading on or below an 8th grade level (SWOG form, 43% [95% CI = 33.0%-53.0%] versus LSU form, 45% [95% CI=35.0%-55.0%]; P<.0001).

Results of the 10 comprehension questions are shown in Table 2. Of note, the participants' comprehension of basic treatment information was very low. For example, less than a third of the participants tested understood the differences in the three treatments for the breast cancer protocol (14% [95% CI = 5.7%-22.3%] for the SWOG form versus 25% [95% CI = 16.9%-33.1%] for the LSU form) or what determines which treatment you get (23% [95% CI = 12.9%-33.1%] for the SWOG form versus 18% [95% CI = 10.8%-25.2%] for the LSU form).

Discussion

Informed consent is an interactive, multifaceted process, of which one important element is the informed consent document. In clinical research, participants must be given informed consent documents that they can understand (6,7,28), yet participants in this study comprehended just over half of the information in the standard SWOG consent form (56%) or in the simplified LSU form (58%). Making the form more suitable by using suggestions from the literature (12,16,18,24-30) and eliciting participant input made the consent document easier to read and less frightening to the participants but did not improve comprehension of the elements contained within it.

The results of this study confirm those of previous studies that showed comprehension of informed consent documents poses problems for many participants. Williams et al. (11) found that fewer than half of participants in public hospitals in Atlanta and Los Angeles could comprehend the standard consent document used for invasive procedures at the Atlanta hospital. Cassileth et al. (24) found that 60% of patients participating in a study conducted in Philadelphia understood the purpose and nature of medical procedures to which they had signed written consent just 1 day before and that only 40% of the participants reported they had read the form carefully. Cassileth et al. (24) concluded that the difficulty of the material and its legalistic wording imposed barriers to the patients' comprehension of information intended to facilitate informed decisions.

To improve comprehension, consent forms should be brief and direct. They should avoid legal jargon and should be written at appropriate reading levels using plain English (12,19). Following these recommendations and those in the participant education literature, we developed a more suitable form written on a 7th grade level. This form was rated as being easier to read than the SWOG form (16th grade level) by the participants in the study, yet their comprehension of the content was not improved. These findings support the results of another study (2), which showed that simplifying informed consent materials alone does not significantly improve participant comprehension. On the other hand, Young et al. (8) reported significantly (P<.OS) higher participant comprehension using a simplified form (6th grade level) compared with a standard form (16th grade level). While the differences reported by Young et al. reached statistical significance, they seem to be of marginal clinical importance: They found a mean difference of only 0.6 more questions (of the 21 questions) answered correctly on the "low reading level consent form." Research is lacking as to the methods by which participant comprehension of informed consent documents can be increased to a clinically acceptable level or even what a clinically acceptable level might be.

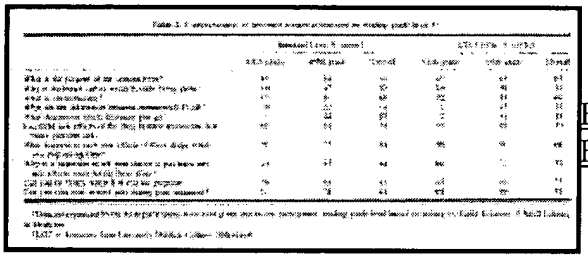

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Table 2.

Our previous research (11,18,25), as well as other research, indicated that participants with very low literacy would probably not be able to adequately comprehend either standard or simplified consent form. Williams et al. (11) suggested that simplifying the text to an approximately 6th grade level might allow marginally literate participants to comprehend the documents. We hypothesized that a form written on a 7th grade level would be better understood by participants with both adequate and marginal literacy levels in comparison to a standard form written on a 16th grade level. We further hypothesized that those who would benefit most from the simplified form would be participants with marginal literacy skills. In actuality, participants with adequate literacy levels (i.e., those reading at or above a 9th grade level) comprehended both forms at marginally adequate levels: 73% the simplified LSU form and 71% the standard SWOG form. Participants with marginal literacy skills (i.e., those reading at a 7th-8th grade level) understood approximately half of the information on either form. Although comprehension was higher with the simplified form, the difference was not statistically significant.

Participants with inadequate literacy skills understood only a minimal amount of the content of either form. Those reading at a 4th-6th grade level comprehended 41% of the LSU form and 35% of the SWOG form. The 17 participants with the lowest literacy, (0-3rd grade reading level), who could be considered functionally illiterate, comprehended only 20% of the LSU form and 10% of the SWOG form. These findings indicate that 1) standard forms do not adequately inform participants (particularly those with marginal and inadequate literacy skills) and 2) simplified forms, when used alone, do not significantly improve the comprehension of participants-at any reading level.

Given that approximately 90 million adults in the United States have inadequate literacy skills (21), our findings raise ethical and legal questions about the ability of informed consent documents to aid all individuals in the decision-making process for study participation. These adults may not be able to read and understand the forms they are signing, and they may not let clinicians or researchers know their problem since most participants who have reading difficulties are embarrassed to admit it (39). Clinicians should also be aware that patients with inadequate literacy skills may be anxious about being expected to read and sign documents and to communicate with physicians (18,34,39). Patients with low literacy may also have problems with basic physician/participant

communication. Recent studies (40,41) have shown that participants with extremely limited literacy skills may have limited health knowledge and may not understand basic health concepts such as the purpose of a mammogram. Such individuals often do not understand what the physician has said and may not be willing to ask physicians for clarification of information (18,39).

In an attempt to sufficiently inform patients so they can make a rational decision about participating in a research study, the Department of Health and Human Services (1) developed detailed regulations concerning the minimum information that consent forms should contain. Subsequently, consent forms have expanded in length (19,23). However, in our study and in other studies, consent forms that are longer and more detailed did not improve the readability of the form or its comprehension by participants (19,23). In this study, participants preferred the shorter, easy-to-read material and found it less frightening. Perhaps long forms written on a college level, though intended to provide complete information for informed consent of a clinical trial, may inadvertently be frightening and overwhelming, especially for low-level readers.

In our study, even those participants who read on at least a 9th grade level were not offended by the simple form. Only seven of 183 participants reported that they were insulted by either form, and none were offended by the simplicity of the LSU form. This observation supports earlier findings (25,26) that neither highly literate nor high-income participants are offended by simple material.

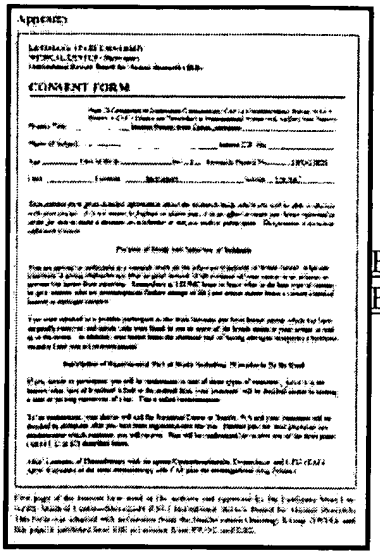
Ethicists and patient educators (8,17,24,42-46) are recommending that patients be included in the development of patient education materials and forms to ensure that the materials include information important to them and are more understandable, appealing, and culturally sensitive. Reid et al. (45) found that patients and physicians differed in what they thought was important to include in written material. This may also be true for informed consent. Turner et al. (46) found that physicians did not identify the outcomes that were most important to cancer patients. For example, patients indicated that acute side effects were as important as long-term side effects. Side effects that were not routinely emphasized, such as energy loss or change in appearance, were more important to patients. Cassileth et al. (24) found that 80% of participants viewed consent forms as a protection for physicians.

In developing the LSU simplified consent form we elicited individual patient feedback on various versions of the form and we modified it over a 2-week period based on this input. While patients liked the information presented in booklet form, they felt it was important for a consent form to look official and they requested a formal cover page and legally detailed signature page. A one-page insert was added as a supplement to the booklet.

There are several limitations to this study. First, although the different consent forms were administered on alternate days, the study was not randomized in the traditional sense. More participants were initially given the LSU form because more questionnaires could be completed in each testing period when the shorter, simplified LSU form was reviewed by participants first. Second, none of the participants were candidates for the phase III breast cancer trial for which the consent form was designed. Therefore, neither the SWOG nor the LSU consent form was specifically relevant to them, and none of the participants were dealing with an actual recent diagnosis of cancer. They did not have to truly consider participation in a clinical trial and, as such, did not have associated anxiety that might interfere with comprehension of both verbal and written communication. Third, in a standard clinical encounter, a written informed consent document is supplemental to an interactive, "face-to-face" consent process. The design of our study did not include this active continuing process. Comprehension was limited to what the participant could understand from reading the document.

Another potential problem is that, although the questionnaire was pilot-tested for comprehension, the validity of the questionnaire was not extensively tested to determine the appropriateness of the questions. In addition, the questions did not assess the participants' comprehension of all eight essential elements of informed consent as outlined by the FDA. The Deaconess Informed Consent Comprehension Test (3), published after this study was conducted, provides 14 questions that could be used to assess all eight elements of informed consent. The design of the study also does not control for previous knowledge and does not distinguish between recall and true comprehension. However, there is no published standard that defines a coherent methodology to test comprehension in a similar setting.

In conclusion, our findings indicate that simplifying informed consent material alone makes the forms more appealing and easier to read but will not improve comprehension. Research is needed to determine the methods to increase comprehension, especially for participants with inadequate or marginal reading skills. Input from participants and recognition of hidden illiteracy will be critical in the development of better informed consent.



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Appendix

[Footnote]
Note
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